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Prognostic Factors of Renal Cell Carcinoma: A Multivariate Analysis

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Background and Objectives: To establish appropriate therapeutic modalities for renal cell carcinoma (RCC), informations on the factors affecting prognosis of patients are essential. For this purpose, multivariate analysis including a large set of variables is necessary.

Methods: Prognostic significance of 14 clinical factors and 19 histologic factors including counting of silver-stained nucleolar organizer regions (AgNORs) were evaluated in 96 patients. Age of patients ranged from 41 to 85 (median 59) yr with a male to female ratio of 4:1. The tumors were staged based on the TNM classification as follows: 7 in stage I, 58 in stage II, 15 in stage III, and 11 in stage IV.

Results: The overall and metastasis-free survival rates in all patients were 80.1% and 72.7%, respectively. Multivariate analysis using Cox's proportional hazards model performed on the factors proved to be significant at the univariate analysis. Univariate analysis revealed four clinical factors including presence of macroscopic hematuria, symptoms such as pain and palpable abdominal mass, anemia, and adjuvant therapy, and nine histologic factors, including AgNOR count, to be significant for survival. Multivariate analysis showed that anemia, pathological stage, and AgNOR count were independent factors for overall survival of patients. The AgNOR count, in particular, is the only predictive factor for metastasis-free survival.

Conclusions: Among various clinicopathological factors, anemia, pathological stage, and AgNOR count are significant prognosticators of RCC. The AgNOR count is also predictive factor for metastasis-free survival.

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KEY WORDS: **renal cell carcinoma; prognostic factors; multivariate analysis; silver-stained nucleolar organizer regions (AgNORs)**

INTRODUCTION

Renal cell carcinoma (RCC) is one of the common cancers in elderly persons not only in Western countries, but also in Japan. Prognosis of patients with RCC is generally unfavorable due to advanced disease even at admission and its resistance to adjuvant therapy. To establish appropriate therapeutic modalities, information on the biologic behavior of RCC, especially factors affecting prognosis of patients, is essential. Several investigators reported weight reduction [1], performance status [1,2], and histologic grade [3–5] to be significant for survival, but others did not [6,7]. Previous studies on the histologic factors suggested that the pathological stage of disease was important for prognosis [2,4,8,9]. Proliferative activity, usually estimated by counting mitotic figures, is generally considered to be an important factor for prognosis of patients with various kinds of cancers. Meanwhile, necrotic and degenerative changes of tumor

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cells are commonly found in RCC, especially after preoperative embolization therapy, thus evaluation of precise cytologic or even histologic features is frequently difficult.

Recently, histochemical and immunohistochemical evaluation of proliferative activity of tumors have been introduced. They include analysis of ploidy pattern and phase of cell cycle by flow cytometry [10], immunohistochemical detection of proliferating cell nuclear antigen (PCNA) [7,10,11], and Ki-67 staining [12–15]. Nucleolar organizer regions (NORs) are intranuclear structures visible on silver-staining of paraffin-embedded histological sections and appear to be associated with synthetic activity within the nucleus in mitotically active cells [16]. The silver-colloid staining method allows light microscopic identification of NORs [17] and permits retrospective study for surgical specimens. Prognostic significance of the AgNOR count in RCC is controversial; some have argued its significance [5,18], but others have not [12,19,20]. We previously reported the usefulness of AgNOR counting in predicting the survival of patients with soft tissue sarcomas [21], in which our own counting method was employed. Subsequently, we showed that the AgNOR count showed a good correlation with the ploidy pattern and stage of the cell cycle [22].

In the current study, a multivariate analysis using Cox's proportional hazards model was performed in 96 patients with RCC to analyze the predictive values of a set of large numbers of clinical and histologic factors, including the AgNOR count.

MATERIALS AND METHODS

Patients

Through a review of clinical and histologic findings in 107 cases of RCC treated at five hospitals situated in Osaka, Japan, during the period 1989–1992, 96 patients were selected for the current study. Eleven cases were excluded because of lack of adequate follow-up data or surgically resected specimens. Clinicopathological evaluations were performed for various characteristics (Table I). Age of the patients ranged from 41 to 85 (median 59) yr with a male to female ratio of 4:1. Symptoms included abdominal mass and/or pain. Anemia defined as a serum hemoglobin level of less than 12 g/dl in males or 11 g/dl in females was found in 72 patients. Total nephrectomy (91 cases) or partial nephrectomy in 5 cases. Histologic specimens were fixed in 10% formalin and routinely processed for paraffin-embedding. Tumor size was divided into two groups according to the greatest diameter: <5.6 cm, which was the median size of all tumors, and >5.6 cm. Histologic sections, cut at 4 μm, were stained with hematoxylin and eosin, and AgNOR staining. The tumors were staged based on the TNM classification of the UICC [23]: the number of patients in stages I, II, III, and IV was 7, 58, 15, and 11, respectively. Forty patients received adjuvant therapy; interferons(IFN)-α and/or γ in 35, tegafur/uracil in 4, and systemic chemotherapy using methotrexate, vincristine, Adriamycin, and cisplatinum in one.

TABLE I. Pathological Characteristics of 96 Patients With Renal Cell Carcinoma*

Characteristics	Characteristics: number of patients
Age	<59:45 ≧59:51
Sex	male:77 female:19
Symptoms	no:68 yes:28
Macroscopic hematuria	no:65 yes:31
Fever	no:93 yes:3
Weight loss	no:87 yes:9
Performance status	0:87 1:4 2:2 3:1
Anemia	no:72 yes:14
Tumor location	left:54 right:41 bilateral:1
Tumor situation	upper:33 middle:24 lower:30
Tumor size	<5.6cm:45 ≧5.6cm:45
Tumor multiplicity	single:93 double:2
Adjuvant therapy	no:55 yes:40
Pathologic stage (UICC)	I:7 II:58 III:15 IV:11
T classification	1:7 2:65 3a:16 3b:3 4:1
N classification	0:92 1:1 2:3
M classification	0:87 1:9
Histologic type	alveolar:53 tubular:9 papillary:9 cystic:16 solid:9
Growth pattern	pushing:68 infiltrative:22
Necrosis	absent:40 moderate:30 marked:21
Sclerosis	absent:52 moderate:32 marked:12
Vascularity	hypovascular:12 hypervascular:84
Capsular invasion	absent:80 present:10
Blood vessel invasion	absent:80 present:11
Lymphangeal invasion	absent:85 present:6
Lymphocyte infiltration	absent:40 mild:39 prominent:14
Intraepithelial dysplasia	absent:91 present:3
Cellularity	low:24 moderate:55 high:17
Cell type	common type:88 clear cell subtype:59 granular cell subtype:15 mixed subtype:14 uncommon cell type:8
Nuclear size	small:23 moderate:58 large:15
Nuclear shape	monomorphic:85 pleomorphic:11
Nucleoli	small:41 prominent:55
Mitosis	absent:50 present:46
Histologic grade	1:27 2:36 3:25 4:8
AgNOR count	<4.4:46 ≧4.4:46

*Data not available for all patients in all cases.

Histologic Analysis

Histologic sections in all 96 cases were reviewed independently by two pathologists (Y.Y. and K.A.). Histologic type and grading of tumors were defined according to the criteria of the World Health Organization [24] and Fuhrman's grading system [25]. In addition, histologic factors such as structural type, growth pattern (pushing or infiltrative), presence of intratubular epithelial dysplasia adjoining the tumor [26], degrees of cellularity, necrosis, sclerosis, vascularity, presence of capsular invasion, vascular and lymphatic invasion, and degree

of lymphocytic infiltration within tumors were evaluated. Degrees of cellularity, necrosis, sclerosis, and lymphocytic infiltration were divided into three grades: low, intermediate, and high or absent, mild, and marked. Cytologic features of tumor cells including size or shape of nucleus, nucleoli, and number of mitosis were also evaluated. Mitotic counts ranged from 0 to 15 per 10 high power fields, without discernible mitotic figures in about a half of the cases.

AgNOR Staining and Counting

AgNOR staining and counting were carried out as previously described [21]. The sections were examined under a 100× oil immersion lens by one of us (Y.Y.) without knowledge of the clinical course of patients. The areas containing the largest number of AgNOR dots were selected for counting, and the numbers of AgNOR dots per nucleus of 200 tumor cells selected randomly were counted. The areas adjacent to prominent necrosis and/or sclerosis were excluded from counting. Subsequently, 100 cells showing the highest AgNOR count were sorted and the mean number per nucleus was calculated. As a control, a section of soft-tissue sarcoma known to have high AgNOR counts was stained for AgNORs. In addition, positive reaction of infiltrated lymphocytes and vascular endothelial cells was used as internal controls.

Statistical Analysis

The follow-up period for survivors, calculated from the date of initial definitive surgical treatment, ranged from 4 to 88 (median 48) mo. Overall and metastasis-free survival curves were calculated using the method of Kaplan and Meier [27], and differences were compared by the log-rank test to analyze the significant prognostic factors [28]. The overall and metastasis-free 5-yr survival rates in all patients were 80.1 and 72.7%, respectively. Multivariate analysis was performed by Cox's proportional hazards model [29], using the SAS program [30] to identify sets of independent prognostic factors for overall and metastasis-free survivals. Prognostic factors, significant at $P < 0.05$ in the proportional hazards model analysis, were selected as being important in influencing survival.

RESULTS

Univariate Analysis

Survival rates for each clinicopathological variable are shown in Table II. The number of patients showing fever, weight loss, poor performance status, multiple tumors, lymphangeal invasion, intraepithelial dysplasia adjoining the tumor, and pM classification was small; thus prognostic value of these factors could not be evaluated.

Age. The age divided by a decade or median age did not affect the survival of the patients.

Sex. There was no difference in survival between male and female patients.

Symptoms. Patients with symptoms such as abdominal palpable mass and/or pain showed a less favorable overall ($P < 0.001$) and metastasis-free survivals ($P < 0.05$) than those without these symptoms.

Hematuria. Patients with macroscopic hematuria at admission showed a less favorable metastasis-free survival than those without, but the difference was not statistically significant ($P = 0.1670$).

Anemia. Patients with anemia showed a less favorable prognosis than those without ($P < 0.01$).

Location of tumor. Tumor location did not affect the prognosis of patients ($P = 0.2273$).

Situation of tumor. Patients with tumors situated at the upper part of the kidney showed a rather favorable prognosis than those with lower part, but the difference was not significant ($P = 0.6792$).

Size of tumor. The prognosis in each group did not differ significantly ($P = 0.5624$).

Pathological stage (TNM classification). The patients with advanced stage (III or IV) diseases showed a more unfavorable prognosis than those with early stage (I or II) ($P < 0.001$).

T classification. Patients with tumors at pT3 or pT4 stage showed a less favorable prognosis ($P < 0.05$ in overall and metastasis-free survival) than those without.

N classification. Patients with lymphnode metastases (pN1-3) showed a less favorable overall prognosis than those without, but the difference was not significant ($P = 0.0657$).

Histologic type. The tumor was classified into five histologic types as follows; alveolar, tubular, papillary, cystic, and solid. The alveolar type was the most common ($n = 53$), followed by the cystic type ($n = 16$). The prognosis in each group did not differ significantly ($P = 0.1908$).

Growth pattern. Tumor margin defined at microscopic level was categorized into two groups, i.e., pushing and infiltrative. Patients with infiltrative margins showed a worse prognosis than those with pushing margins ($P < 0.001$).

Capsular invasion. Patients with capsular invasion of tumors (10 cases) showed a less favorable prognosis ($P < 0.05$ in overall and metastasis-free survival) than those without.

Cellularity. Patients with highly cellular tumor showed a worse prognosis than those with lower cellularity ($P < 0.001$).

Cell type. Cytologic features were categorized into two groups: common type including clear cell, granular cell, and mixed cell types and uncommon type (8 cases) including spindle and pleomorphic cell types. Patients with clear cell subtype showed the most favorable prognosis than those with other types ($P < 0.01$ in overall and metastasis-free survival).

TABLE II. Univariate Analysis for Clinicopathological Factors in Renal Cell Carcinoma

		5-yr survival rates (%)			
Factor	No. of patients	Overall	*P* value	Metastasis free	*P* value
Age (yr)					
<59	45	81.5		74.5	
⩾59	51	79.6	NS	72.5	NS[a]
Sex					
Male	77	79.7		72.9	
Female	19	83.1	NS	72.2	NS
Symptoms					
No	68	88.0		78.2	
Yes	28	58.3	<0.001	59.1	<0.05
Macroscopic hematuria					
No	65	87.5		82.0	
Yes	31	67.6	NS	55.4	NS
Anemia					
No	72	85.9		78.2	
Yes	14	55.3	<0.01	53.0	<0.01
Tumor location					
Left	54	86.6		80.1	
Right	41	72.4	NS	63.5	NS
Tumor situation					
Upper	33	73.7		68.6	
Lower	30	92.6	NS	79.6	NS
Tumor size (cm)					
<5.6	45	79.9		76.7	
⩾5.6	45	85.4	NS	73.9	NS
Pathologic stage					
UICC I, II	65	93.0		85.1	
III, IV	26	46.4	<0.001	39.4	<0.05
T classification					
pT1-2	72	86.2		78.9	
pT3a-4b	20	61.4	<0.05	51.9	<0.05
N classification					
pN0	92	81.5		73.4	
pN1-3	4	50.0	NS	50.0	NS
Histologic type					
alveolar type	53	83.4		74.4	
other types	43	76.9	NS	71.4	NS
Growth pattern					
Pushing	68	88.3		81.6	
Infiltrative	22	53.8	<0.001	44.1	<0.001
Necrosis					
Absent	40	84.9		81.0	
Present	51	76.6	NS	66.8	<0.05
Sclerosis					
Absent	52	74.1		65.8	
Present	44	86.0	NS	79.5	NS
Vascularity					
Hypovascular	12	81.5		72.9	
Hypervascular	84	80.4	NS	72.9	NS
Capsular invasion					
Absent	80	82.4		74.9	
Present	10	58.3	<0.05	48.0	<0.05
Blood vessel invasion					
Absent	80	81.4		75.7	
Present	11	68.2	NS	42.4	NS
Lymphocyte infiltration					
Absent	40	86.9		82.5	
Present	53	73.3	NS	63.1	NS

(*continued*)

TABLE II. Univariate Analysis for Clinicopathological Factors in Renal Cell Carcinoma (*Continued*)

Factor	5-yr survival rates (%)				
	No. of patients	Overall	*P* value	Metastasis free	*P* value
Cellularity					
low or moderate	79	86.8		78.1	
High	17	51.1	<0.001	47.3	<0.01
Cell type					
Clear cell subtype	59	91.5		83	
Other types	37	62.0	<0.01	56.7	<0.01
Nuclear size					
low or moderate	81	85.3		77.0	
Large	15	49.9	<0.001	48.2	<0.01
Nuclear shape					
Monomorphic	85	86.3		78.3	
Pleomorphic	11	30.5	<0.001	24.0	<0.001
Nucleoli					
Small	41	84.1		81.7	
Prominent	55	78.2	NS	66.6	NS
Mitosis					
Absent	50	87.8		80.2	
Present	46	70.3	NS	64.6	NS
Histologic grade					
low(1-2)	63	86.3		80.9	
high(3-4)	33	69.3	<0.05	58.4	<0.01
AgNOR count					
<4.4	46	95.2		95.2	
≧4.4	46	66.0	< 0.01	50.6	<0.001

[a]NS, not significant.

Nuclear size. The tumor cell nuclear size was defined in comparison with the size of erythrocyte as follows: almost equal size, larger but less than three times, and more than three times larger. Patients with tumor cell nuclei three times larger than erythrocyte showed a worse prognosis than those with less large nuclei ($P < 0.001$ in overall, $P < 0.01$ in metastasis-free survival).

Nuclear shape. Tumor cells were divided into two groups: monomorphic and pleomorphic. Patients with pleomorphic nuclei showed a worse prognosis than those with monomorphic nuclei ($P < 0.001$ in overall and metastasis-free survival).

Histologic grade. Patients with high grade (3 or 4) tumor showed a worse prognosis than those with low grade (1 and 2) tumors ($P < 0.05$ in overall, $P < 0.01$ in metastasis-free survival).

AgNOR count. The median AgNOR count was 4.4. Patients were divided into two groups: high count group (mean AgNOR count >4.4 per nucleus; Fig. 1a) and low count group (<4.4; Fig. 1b). Patients with low AgNOR count had a more favorable prognosis than those with high count ($P < 0.01$ in overall, $P < 0.001$ in metastasis-free survival).

Multivariate Analysis

Thirteen clinicopathological factors, including symptoms, anemia, and pathological stage, which included T-classification, growth pattern, necrosis, capsular invasion, cellularity, cell type, nuclear size, nuclear pleomorphism, histologic grade, and AgNOR count, were significant for survival at the univariate analysis: 12 in overall and 13 in metastasis-free survival. These factors were selected for the multivariate analysis. The results of multivariate analysis are shown in Table III. Anemia, pathological stage, and AgNOR count proved to be the independent factors significant for overall survival of patients. AgNOR count was the only independent factor for metastasis-free survival (Fig. 2).

DISCUSSION

Median age of 59 yr and male preponderance found in the present cases were similar to those in the previous reports [1,15,19]. Approximately 70% (65/91) of patients had stage I and II disease with the 5-yr survival rate of 89.2%, quite similar to those reported previously [8].

The univariate analysis of clinical factors in the current series revealed similar results to those reported previously [8], i.e., symptoms, hematuria, and anemia were significant for survival of patients [31–33]. Among the classical triad of RCC, i.e., fever, hematuria, and pain, the latter two were important prognostic factors. Age [34], gender [31,35], weight loss [1,34], performance status [1,2], and tumor location and size [7,36] were reported to be ominous prognostic factors in the previous

TABLE III. Multivariate Analysis for Prognostic Factors in 96 Patients With Renal Cell Carcinoma

Variables	Category	Overall survival		Metastasis-free survival	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Symptom	0:asymptomatic, 1:symptomatic	7.075 (0.675–104.013)	0.1047	3.303 (0.748–13.872)	0.1116
Anemia	0:within normal range, 1:anemic	14.919 (1.559–230.10)	0.0180	2.547 (0.620–11.372)	0.1923
Pathological stage	0: I or II, 1: III or IV	10.426 (1.821–97.269)	0.0077	3.489 (0.977–12.846)	0.0543
Growth pattern	0:pushing, 1:infiltrative	1.508 (0.120–15.539)	0.7395	2.235 (0.581–8.405)	0.2345
Capsular invasion	0:absent, 1:present	0.207 (0.011–2.147)	0.1903	0.830 (0.150–4.308)	0.8234
Cellularity	0:low or moderate, 1:high	3.668 (0.362–49.066)	0.2753	1.080 (0.194–5.697)	0.9268
Necrosis	0:absent, 1:present	–	–	1.978 (0.515–8.753)	0.3237
Clear cell subtype	0:clear cell subtype, 1:other types	0.493 (0.059–3.994)	0.4849	0.362 (0.078–1.742)	0.1971
Nuclear size	0:low or moderate, 1:high	0.116 (0.002–3.600)	0.2338	0.876 (0.095–6.075)	0.8971
Nuclear shape	0:monomorphic, 1:pleomorphic	7.264 (0.242–359.292)	0.2556	0.560 (0.056–4.517)	0.6311
Histologic grade	0:1 or 2, 1:3 or 4	0.504 (0.039–4.503)	0.5453	1.156 (0.214–5.907)	0.8619
AgNOR count	0:<4.4, 1:≧4.4	11.575 (1.493–311.417)	0.0162	9.308 (2.092–71.694)	0.0023

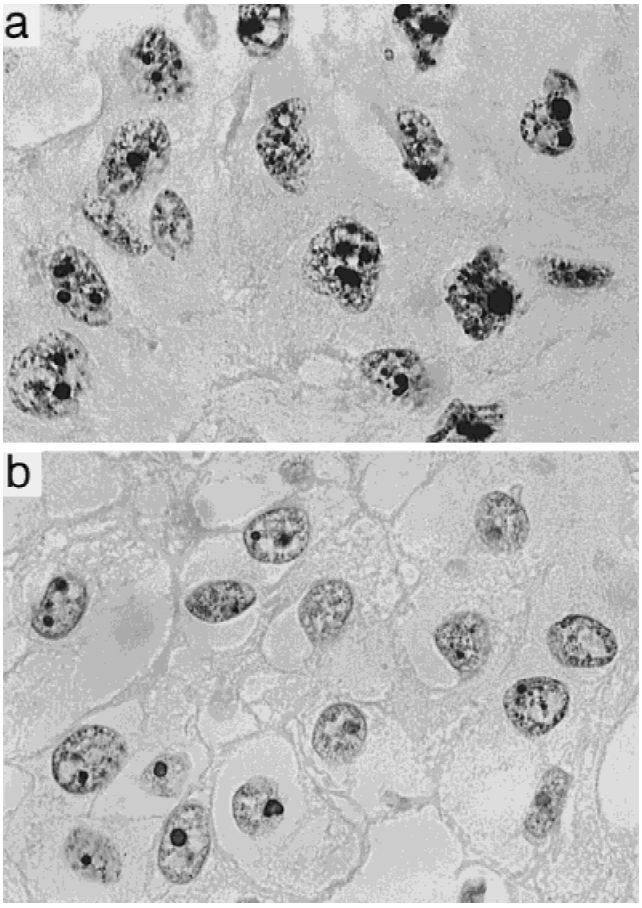

Fig. 1. AgNOR staining of **(a)** high count and **(b)** low count group. Numerous dots are found in the nucleus of high count case (×2500).

literature using univariate analysis. However, the current multivariate analysis revealed all these factors not to be independent factors significant for survival. In the current study, a large number of clinicopathologic variables were included in the analysis, lending credibility to the results.

As for histologic parameters, tumor grade, nuclear pleomorphism, mitotic counts, growth pattern of the tumor, cytoplasmic granularity, and thickness of pseudocapsule surrounding the tumors have been reported to be prognostic factors for RCC [37,38]. The current study showed that the histologic factors, including pathological stage, cellularity, cell type, nuclear size, and AgNOR count together with those reported previously, were significant factors for prognosis [2,4,5,8,9,18]. Infiltrative margin and capsular invasion, suggestive of invasiveness of the tumor, also affected the prognosis of the patients. Mancilla-Jimenez et al. [39] reported that patients with papillary RCC showed a more favorable prognosis than those with nonpapillary carcinomas, although other reports gave contradictory results [25,40,41]. The current study showed similar results to that of Mancilla-Jimenez et al. [39], but the difference was not significant ($P = 0.2133$). Alternatively, solid pattern of proliferation was a sign for an unfavorable course in the present study.

With regard to cytologic features, all patients with an uncommon cell type such as spindle and pleomorphic cells, or so-called sarcomatoid cell type, died within 5 yr. Poor survival of the sarcomatoid RCC was explained by its aggressive biologic behavior because of the high proliferative activity [42] and high mutation rate of the *p53* gene [43]. Histologic grade was a factor affecting the prognosis of patients as reported previously [3,4,25]: patients with grade 3 or 4 tumors showed a less favorable prognosis than those with grades 1 or 2. Histologic grading was mainly defined by the combination of cytologic features, including the enlargement and pleomorphism of nucleus and nucleolus. In the current analysis, the nuclear features correlated with survival, but the nucleoli did not. The mitotic counts, supposed to influence the histologic grading, did not correlate with prognosis in the current patients. Severe ischemic change in the tumors was common in RCC, which might have made the objective estimation of mitotic figures difficult.

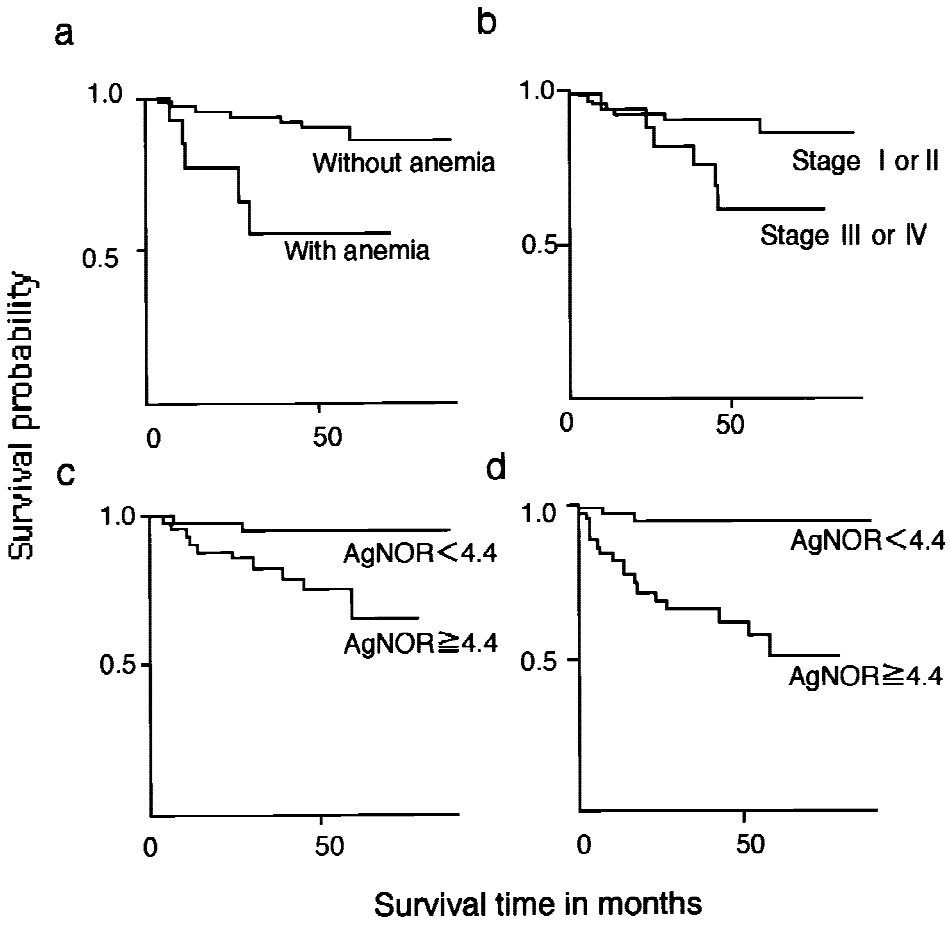

Fig. 2. Five-yr overall survival of patients with **(a)** anemia ($P < 0.01$) and **(b)** advanced stage disease (III, IV) ($P < 0.001$) showed a less favorable prognosis than those without. Patients with a high AgNOR count showed a less favorable prognosis in **(c)** overall ($P < 0.01$) and **(d)** metastasis-free ($P < 0.001$) 5-yr survivals than those without.

Multivariate analysis revealed that the majority of variables significant at the univariate analysis were not independent factors affecting survival of patients. Anemia, pathological stage, and AgNOR count proved to be significant for overall survival of patients. Especially, AgNOR count was the most significant factor for metastasis-free survival. The mean AgNOR count in each grade was 2.81 in grade 1, 4.67 in 2, 5.85 in 3, and 7.68 in 4, respectively. These values in each grade of RCC were similar to those in the previous report using the same counting method [18]. Other markers detecting proliferative activity such as proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1) index might be useful for predicting the prognosis [9,12–15]. However, previous reports on PCNA staining in RCC gave conflicting results [7,9]. Ki-67 index proved to be a useful prognostic indicator for RCC [9,13], although it can be used only on fresh-frozen sections. Immunohistochemical staining of MIB-1, which detects the Ki-67 antigen on paraffin-embedded specimens, is now possible and has been proven to be a prognostic marker [12,14,15].

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